PATENT SPECIFICATION (11) 1 492 528

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(21) Application No. 15644/76 (22) Filed 15 April 1976
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(33) United States of America (US)
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(51) INT CL² C07D 403/04//241/14 (C07D 403/04, 241/04, 241/24)
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C2C 1620 1626 215 220 226 22Y 246 247 248 250 252 258 25Y 280 281 28X 29X 29Y 305 30Y 311 313 314 31Y 321 323 326 32Y 334 337 338 339 342 34Y 350 351 355 35Y 364 366 367 368 36Y 373 37X 37Y 386 401 40Y 43X 440 456 45Y 464 490 500 50Y 54X 551 55X 574 579 584 601 613 614 620 624 625 628 62X 62Y 634 63Y 656 65X 662 670 672 675 676 678 694 699 69Y 73Y 775 776 77Y 790 79Y BG BK KF NB NG NR QM TA UJ WH WK YX ZB ZL

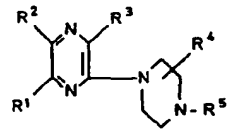
(72) Inventors WALFRED SPENCER SAARI and WILLIAM CARL LUMMA JR.

(54) PYRAZINYL PIPERAZINE DERIVATIVES

(71) We, MERCK & CO. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Obesity is a fairly common condition and a potentially serious one in view of the correlation between incidence of various diseases and the degree to which a person is overweight. For example, obese persons succumb statistically more frequently to cardiovascular renal disease than do persons of normal weight. Obesity likewise results in higher death rates from diabetes, nephritis, pneumonia, cirrhosis, appendicitis and postoperative complications. Since obesity often occurs simply as a consequence of excessive intake of calories, good management of th condition in these cases can be achieved by restricting the caloric intake. Frequently, however, the patient has difficulty in initiating and maintaining dietary restrictions, making it necessary to use anorexigenic drugs as adjuvants to therapy.

The piperazinylpyrazine compounds useful in the novel method of treatment of the present invention have the structural formula:



in which R^1 is hydrogen, halogen (F, Cl, Br or I), C_{1-3} haloalkyl, C_{1-4} alkoxy,

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The following corrections were allowed under Section 76 on 21 April 1978

Page 16, line 38, *after* containing *delete* as active ingredient *after* and *insert* as active ingredient

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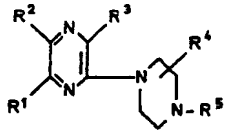
The piperazinylpyrazine compounds useful in the novel method of treatment of the present invention have the structural formula:



in which R^1 is hydrogen, halogen (F, Cl, Br or I), C_{1-3} haloalkyl, C_{1-4} alkoxy, amino, C_{1-7} alkylthio, phenylthio carbamoyl, (C_{1-4} alkyl)carbamoyl, (C_{1-5} alkoxy) carbonyl, C_{2-6} dialkylamino, phenyl, or phenyl substituted by halogen (F, Cl, Br, or I), by C_{1-4} alkyl or by C_{1-3} alkoxy;

R^2 is hydrogen, halogen (F, Cl, Br or I), alkyl of from 1 to 3 carbon atoms, cyano, amino, (C_{1-5} alkoxy) carbonyl, carbamoyl, alkoxy of from 1 to 4 carbon atoms, haloalkyl of from 1 to 3 carbon atoms, phenyl or substituted phenyl wherein the substituent is halogen (F, Cl, Br or I);

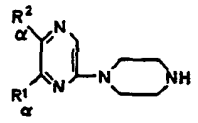
R^3 is hydrogen, halogen (F, Cl, Br, or I), alkanoylamino of from 1 to 3 carbon atoms, carbamoyl, phenyl or phenyl substituted by halogen (F, Cl, Br or I), by alkyl of from 1 to 4 carbon atoms or by alkoxy from 1 to 3 carbon atoms;

R^4 is hydrogen, alkyl of from 1 to 3 carbon atoms, carboxyl or (C_{1-5} alkoxy) carbonyl;

R^5 is hydrogen or alkanoyl of from 1 to 3 carbon atoms; and
the N-oxides and the acid addition salts of the foregoing compounds.

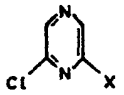
Preferably, R^1 and R^2 are as defined above and R^3 is hydrogen, particularly when one of R^1 and R^2 is also hydrogen.

The novel compounds of the present invention have the structural formula:



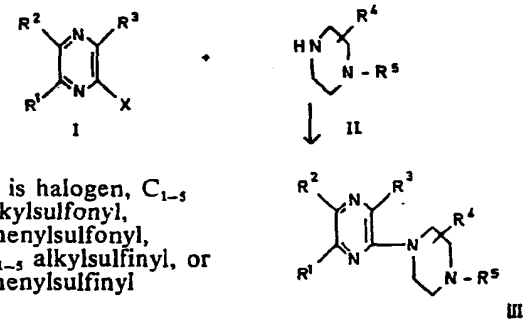
or pharmaceutically acceptable salt thereof, where R^1_α is hydrogen, halogen, especially chlorine, C_{1-4} alkoxy, such as methoxy, trifluoromethyl, C_{2-6} dialkylamino or phenylthio; R^2_α is hydrogen, halogen, especially chlorine, or phenyl, with the proviso that R^1_α and R^2_α are not both hydrogen.

The compounds useful in the novel method of treatment of the present invention, which have formula III, or are N-oxides or acid-addition salts of such compounds, are prepared by reaction of a 2-X-pyrazine of formula I or an N-oxide or acid-addition salt of such a compound with piperazine or a substituted piperazine of formula II (where R^4 and R^5 are as defined above). The novel compounds of the present invention can of course be made by this reaction by choice of suitable values of the variable radicals. For example 6-chloro-2-piperazinylpyrazine may be prepared by reaction of a compound of formula:



where X is as defined below, with piperazine at a temperature in the range 15 to 90°C.

The reaction sequence, showing the free base forms of compounds I and III rather than the N-oxide or a salt, is as follows:



I

II

X is halogen, C_{1-5} alkylsulfonyl, phenylsulfonyl, C_{1-5} alkylsulfinyl, or phenylsulfinyl

III

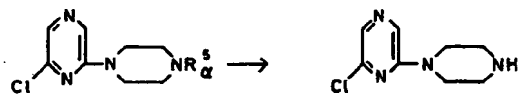
The reaction takes place at temperatures ranging from 15°C to 90°C., preferably under an inert atmosphere, e.g. N_2, He or Ar, until a substantial amount of desired adduct of formula III is obtained, typically for a period of from 0.5 to 6 hours, preferably from 1 to 4 hours.

Where R^5 is to be a C_{1-3} alkanoyl radical, the compound may be prepared by alkanoylating in known manner the corresponding compound in which R^5 is hydrogen.

If a compound in which R^4 is carboxy is desired, it may be obtained by acid hydrolysis of the corresponding compound in which R^4 is alkoxycarbonyl.

Other processes by which 6-chloro-2-(1'-piperazinyl)pyrazine, a particularly preferred compound of this invention, can be prepared are as follows:

I. Removal of Nitrogen Protective groups



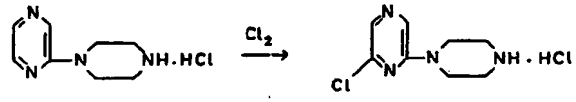
where R_α^5 is a heterocycle such as 6-chloro-2-pyrazinyl; alkanoyl such as formyl or acetyl; aroyl such as benzoyl or *p*-methoxybenzoyl; alkoxycarbonyl, alkenoxycarbonyl, aralkoxycarbonyl or aryloxycarbonyl such as benzyloxycarbonyl, *t*-butoxycarbonyl, phenoxycarbonyl, vinyloxycarbonyl; cyano; carbamoyl, N-alkyl carbamoyl, or N-arylcarbamoyl; aralkyl such as benzyl; or alkyl such as methyl.

Removal of these groups (except aralkyl and alkyl) is effected by hydrolysis in polar solvents in the presence of acid or base.

The alkyl groups and aralkyl groups can be removed by reaction with cyanogen bromide, an alkoxycarbonyl halide, or an aryloxycarbonyl halide to give compounds in which R_α^5=cyano, alkoxycarbonyl, or aryloxycarbonyl, respectively, and subsequently removing these groups as above or below.

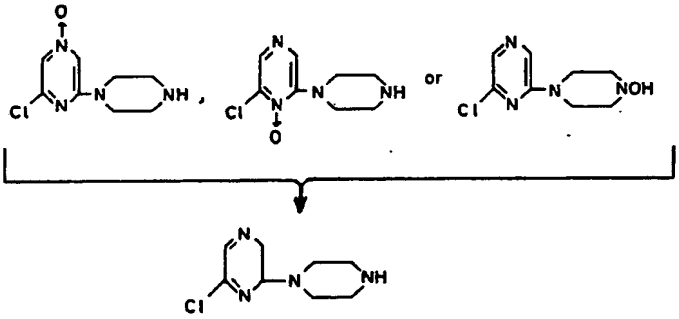
Removal of aralkyl or aralkoxycarbonyl can alternatively be effected by catalytic hydrogenolysis. This may be carried out in nonpolar or polar solvents such as water or alcohols in the presence of catalysts such as Pt, Pd, Ru and oxides thereof at from 25°C. to the reflux temperature.

II. *Chlorination*



The process is conveniently effected by passing Cl_2 gas through a solution of the piperazinyl-pyrazine in a solvent such as glacial acetic acid at a temperature of from 0 to 100°C. Other solvents which can be used are aqueous hydrochloric acid, dimethylformamide, and acetonitrile.

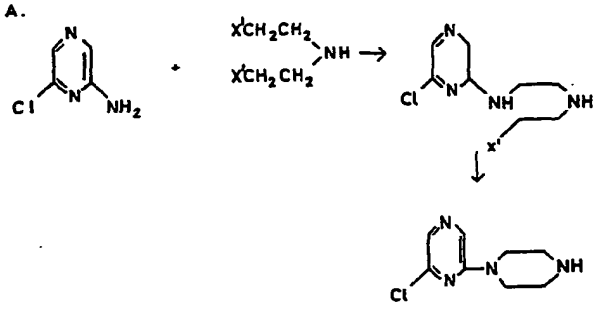
III. *Reduction of N-hydroxy and N-oxide Intermediates*



Suitable reducing agents are tin, zinc, iron, or sulfur-dioxide in inorganic or organic acids; triphenylphosphine, sodium arsenite, ammonium sulfide, sodium dithionite, and ferrous-oxalate-granulated lead; or the reduction may be effected by catalytic hydrogenation, e.g. over palladium on carbon or Raney nickel. Suitable solvents include polar solvents such as water, acetic acid and C_{1-6} alcohols. The reduction is preferably conducted at from 0 to 150°C.

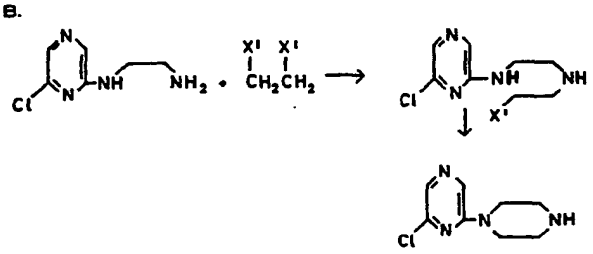
IV. *Formation of the Piperazine Ring*

A.



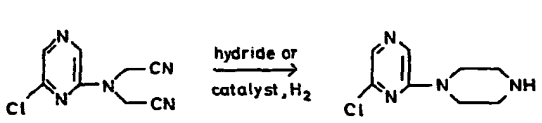
wherein X′ is a displaceable group or atom such as halogen, tosyloxy, mesyloxy, hydroxy, amino, and trialkylammonium. Usually, the above process is effected by heating the reactants at from 0 to 250°C. in a polar solvent such as water, dimethylformamide or alcohols in the presence of base.

B.



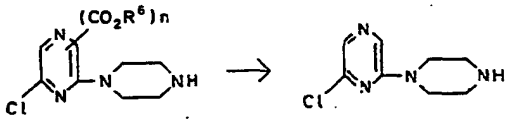
where X′ and process conditions are as described in IVA. above

C.



Suitable catalysts are Raney nickel, copper-chromium oxide, platinum, palladium and oxides thereof in a polar solvent such as aqueous acid or alcohol. Suitable hydrides are borane and lithium aluminium hydride in a nonpolar solvent such as tetrahydrofuran or diethyl ether. The reactions are preferably carried out at a temperature of from −70°C. to 300°C. and a pressure of from 1.0 to 300 atmospheres.

V. *Removal of carboxy or esterified carboxy groups*

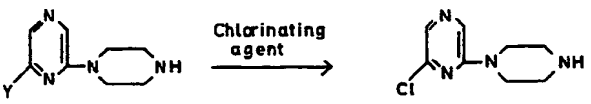


n=1 or 2; R^6=H, alkyl or aralkyl.

The removal is effected by hydrolysis and/or heating. Hydrolysis may be effected in the presence of acid or base in a polar solvent such as water, C_{1-6} alcohols or glymes at a temperature of from 0 to 150°C; heating may take place without solvent or in solvents such as hydrocarbons such as tetrahydronaphthalene, aromatic hydrocarbons, and substituted aromatic solvents such as chlorobenzene or nitrobenzene at a temperature of from 100 to 300°C.

VI. *Introduction of Chlorine by displacement or rearrangement*

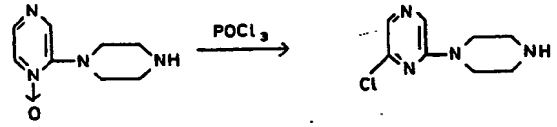
A.



in which Y is hydroxy or alkoxy. The chlorinating agent is preferably BCl_3, $POCl_3$, or PCl_3 and it may also serve as solvent.

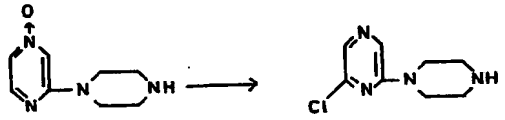
Reaction temperatures are preferably from 25°C. to reflux temperature of the solvent. Mixtures of the above reagents may also be used.

B.



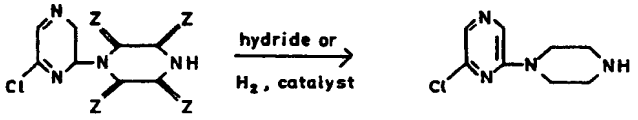
Reaction conditions are the same as those given above.

C.



Benzenesulfonyl chloride is usually used for this reaction under the same conditions as described above.

VII. *Reduction of Amides and Imides*



Z=H_2 or O, at least one 2 being O.

Suitable reducing agents include hydrides such as borane or lithium aluminum hydride, or catalysts such as molybdenum sulfide, copper chromium oxide, ruthenium and platinum oxide. Suitable solvents for catalytic hydrogenation include polar solvents such as water, lower alcohols, glymes and dioxane. Reduction with hydrides, however, is conducted in aprotic solvents, such as diethyl ether and tetrahydrofuran. The reaction temperature is in the range −70°C. to 250°C. at a pressure of from 1.0 to 300 atmospheres.

The compounds of the present invention may be administered as anorexic agents to mammalian species, e.g. rats and mice, in amounts ranging from 0.01 to 20 mg. per kg. of body weight, preferably from 0.1 to 10 mg. per kg. of body weight in a single dose or in 2 to 4 divided doses.

The compounds of the present invention in the described dosages may be administered orally; however, other routes such as intraperitoneally, subcutaneously, intramuscularly, or intravenously may be used.

The active compounds of the present invention are orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, pills, capsules, elixirs, suspensions, syrups, waters or chewing gum. The amount of active compound in

such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

The tablets, troches, pills of capsules, may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch or alginic acid; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit, for instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts used.

As to the pharmaceutically acceptable salts, those coming within the purview of this invention include the pharmaceutically acceptable acid-addition salts. Acids useful for preparing these acid-addition salts include, inter alia, inorganic acids, such as the hydrohalic acids (e.g., hydrochloric and hydrobromic acid), sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as maleic, fumaric, tartaric, citric, acetic, benzoic, 2-acetoxybenzoic, salicylic and succinic acids, theophylline, 8-chlorotheophylline and *p*-aminobenzoic, *p*-acetamidobenzoic, or methanesulfonic acids.

The compounds of the present invention show enhanced effectiveness and less toxicity than known anorexic agents. The 6-chloro-2-(1'-piperazinyl)pyrazine compound, for example, is 10 times as effective as fenfluramine in the cat following oral administration.

In addition to the anorexic activity described above, the novel compounds of this invention pharmacologically influence serotonin levels in a manner that suggests that they are also useful as antidepressant, anti-hypertensive, analgesic and sleep-inducing agents. For these purposes, the same routes of administration, and pharmaceutical formulations as described above would be used.

The following examples illustrate the present invention. Unless otherwise indicated, all temperatures are expressed in degrees Celsius, percentages are on a volume basis where they refer only to liquids and on a weight basis otherwise, and mesh and screen sizes are U.S. standards.

EXAMPLE 1.

6-Chloro-2(1'-piperazinyl)pyrazine hydrochloride

2,6-Dichloropyrazine (0.10 mole) is added to 20 g. piperazine in 200 ml. acetonitrile and the mixture is refluxed for 1.5 hr. under N_2. The mixture is concentrated *in vacuo* and the residue partitioned between 1N aqueous NaOH and benzene. The combined benzene extracts are washed with 1N aqueous NaOH, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a yellow oil which is dissolved in 200 ml. absolute ethanol containing 10 ml. of cold, saturated anhydrous ethanolic HCl. The precipitated hydrochloride is recrystallized from 95% ethanol to give faintly yellow needles, m.p. 350° dec.

EXAMPLE 2.

6-Chloro-2-(4'-acetyl-1'-piperazinyl)-pyrazine

6-Chloro-2-(1'-piperazinyl)-pyrazine hydrochloride (0.064 mole) from Example 1 is dissolved in 250 ml. ice water containing 20 g. sodium acetate trihydrate and the rapidly stirred solution treated with 15 ml. acetic anhydride. After 3 hours the mixture is extracted with benzene, the benzene dried and filtered, and the solvent replaced by *n*-butylchloride. Crystallization gives the title compound, m.p. 106—107.5°.

EXAMPLE 3.

5-Chloro-2-(1'-piperazinyl)-pyrazine hydrochloride

The title compound, m.p. 301—302°, is prepared similarly to Example 1 by substituting 2,5-dichloropyrazine for 2,6-dichloropyrazine.

EXAMPLE 4.

6-Trifluoromethyl-2-(1'-piperazinyl)-pyrazine hydrochloride

2-Pyrazinoic acid (25 g, 0.20 mole) is converted to 2-trifluoromethylpyrazine by h ating with sulfur tetrafluoride (54 g.) at an initial pressure of 160 psi and 150° in a stainless steel autoclave for 6 hours. After quenching the reaction mixture on ice and adding sufficient NaOH to adjust the pH to 6, the crude product is extracted into methylene chloride. Distillation gives 2-trifluoromethylpyrazine, b.p. 118°. The freshly distilled 2-trifluoromethylpyrazine (15.9 g.) is converted to the 4-N-oxide with 30 ml. glacial acetic acid and 20 ml. 30% aqueous hydrogen peroxide for 48 hours at 70°. After quenching the reaction mixture on ice, the product is extracted into benzene. The benzene extracts are washed with aqueous sodium carbonate, dried (Na_2SO_4) and concentrated *in vacuo* to give the crystalline 4-N-oxide, m.p. 57—59°. The N-oxide (3.28 g.) is rearranged nearly exclusively to 2-chloro-6-trifluoromethylpyrazine, b.p. 115° (25 in. Hg) by heating with 5 ml. benzenesulfonylchloride for 4 hours at 100° and distilling the reaction mixture.

The title compound, m.p. 292—294°, is prepared similarly to Example 1, starting from the 2-chloro-6-trifluoromethylpyrazine prepared as described above.

EXAMPLE 5.

6-Methoxy-2-(1'-piperazinyl)-pyrazine dihydrochloride

2,6-Dichloropyrazine (0.067 mole) is treated with a solution of sodium methoxide (0.067 mole) in 100 ml. dry methanol for 1 hour at 25°. The solvent is removed *in vacuo* and the residue is extracted with boiling hexane extract. 2-Chloro-6-methoxypyrazine crystallizes from the hexane extract. Another recrystallization from isopropanol at −70° gives 2-chloro-6-methoxypyrazine as an oil at room temperature.

The title compound, m.p. 189—191°, is prepared similarly to Example 1, using the 2-chloro-6-methoxypyrazine prepared as described above in place of 2,6-dichloropyrazine.

EXAMPLE 6.

6-Chloro-2-(1'-piperazinyl)-pyrazine-1-oxide

2-Chloropyrazine (0.1 mole) is added to a solution of 0.3 mole trifluoroperacetic acid in CH_2Cl_2 (300 ml.) at 0°C. The mixture is stirred for 4 hours at 0°, 4 hours at 25° and finally at reflux for 4 hours. The resulting solution is washed with saturated aqueous NaCl solution and then saturated aqueous Na_2CO_3 solution and concentrated *in vacuo* to give crude 2-chloropyrazine-1,4-dioxide.

The crude 2-chloropyrazine-1,4-dioxide, 20 g., is stirred for 4 hours with 50 ml. benzenesulfonyl chloride at 50° under N_2 and quenched on a mixture of ice, pyridine and saturated NaCl solution. The precipitated 2,6-di-chloropyrazine-1-oxide is collected by filtration and converted to the title compound by reaction with piperazine as in Example 1.

EXAMPLE 7.

6-Chloro-2-(1'-piperazinyl)-pyrazine-4-oxide

In a similar manner to that of Example 6, 2,6-dichloropyrazine is converted to the 4-oxide with 1.8 molar equivalents of trifluoroperacetic acid. The crude 2,6-dichloropyrazine-4-oxide is converted to the title compound by reaction with piperazine as in Example 1.

EXAMPLES 8—23.

Following the procedure of Example 1, the following substituted halopyrazines are reacted with piperazine in acetonitrile to give the corresponding 2-(1'-piperazinyl)-pyrazine derivatives.

Example	Starting Material	Product
8	2,3-Dibromopyrazine	3-Bromo-2-(1'-piperazinyl)-pyrazine hydrochloride
9	2,6-Dibromopyrazine	6-Bromo-2-(1'-piperazinyl)-pyrazine hydrochloride
10	2-Chloro-3,5-diphenylpyrazine	3,5-Diphenyl-2-(1'-piperazinyl)-pyrazine hydrochloride

Example	Starting Material	Product
11	2-Chloro-3,6-diphenylpyrazine	3,6-Diphenyl-2-(1'-piperazinyl)-pyrazine hydrochloride
12	2-Chloro-5,6-diphenylpyrazine	5,6-Diphenyl-2-(1'-piperazinyl)-pyrazine hydrochloride
13	6-Carbamoyl-2-chloropyrazine	6-Carbamoyl-2-(1'-piperazinyl)-pyrazine hydrochloride
14	2-Chloro-6-diethylcarbamoylpyrazine	6-Diethylcarbamoyl-2-(1'-piperazinyl)-pyrazine hydrochloride
15	6-Methoxycarbonyl-2-chloropyrazine	6-Methoxycarbonyl-2-(1'-piperazinyl)-pyrazine hydrochloride
16	5-Carbamoyl-2-chloropyrazine	5-Carbamoyl-2-(1'-piperazinyl)-pyrazine hydrochloride
17	2-Chloro-5-methoxy pyrazine	5-Methoxy-2-(1'-piperazinyl)-pyrazine hydrochloride
18	2-Chloro-5-trichloromethylpyrazine	5-Trichloromethyl-2-(1'-piperazinyl)-pyrazine hydrochloride
19	2-chloro-5-phenylpyrazine	5-phenyl-2-(1'-piperazinyl)-pyrazine hydrochloride, m.p. 304—308°C (dec)
20	2-chloro-6-phenylthiopyrazine	6-phenylthio-2-(1'-piperazinyl)-pyrazine hydrochloride, m.p. 221—222°C.
21	2-Chloro-5-cyanopyrazine	5-Cyano-2-(1'-piperazinyl)-pyrazine hydrochloride
22	2-Chloro-5-(p-chlorophenyl)-pyrazine	5-(p-chlorophenyl)-2-(1'-piperazinyl)-pyrazine hydrochloride
23	5-Amino-2-chloropyrazine	5-Amino-2-(1'-piperazinyl)-pyrazine hydrochloride

EXAMPLE 24.

6-Dimethylamino-2-(1'-piperazinyl)-pyrazine.

20 millimoles (3.14 g) of 6-(N,N-dimethylamino)-2-chloropyrazine and 3 g. of piperazine are fused under nitrogen at 135° for 6 hours. The mixture is dig sted with water and, after being filtered to remove insoluble material, is made alkaline with 10*N* sodium hydroxide and extracted with chloroform. The combined chloroform extracts are washed with 2*N* sodium hydroxide, dried (anhydrous sodium sulfate), filtered and concentrated to an oil under reduced pressure. The product is isolated as the dihydrochloride salt, M.P. 249—250°C, from isopropanol.

EXAMPLES 25—32.

The 2-hydroxypyrazine derivatives (0.10 mole) listed below are converted to the corresponding substituted 2-chloropyrazines by reaction with 0.40 mole phosphorus oxychloride and 10 ml. N,N-dimethylformamide at reflux for 1—4 hours. After quenching the reaction mixture on ice, the substituted 2-chloropyrazine is isolated by extraction into diethyl ether or benzene or by crystallization of the separated product. The 2-chloropyrazine derivatives in turn are converted to the corresponding 2-(1'-piperazinyl)-pyrazine derivatives by reaction with piperazine following the procedure of Example 1.

Example	Starting Material	Product
25	3,6-Di-(4-bromophenyl)-pyrazinol	3,6-Di(4-bromophenyl)-2-(1'-piperazinyl)-pyrazine hydrochloride
26	3,6-Di-(4-butylphenyl)-pyrazinol	3,6-Di-(4-butylphenyl)-2-(1'-piperazinyl)-pyrazine hydrochloride
27	3,6-Di-(4-methoxyphenyl)-pyrazinol	3,6-Di-(4-methoxyphenyl)-2-(1'-piperazinyl)-pyrazine hydrochloride
28	3-Acetamidopyrazinol	3-Acetamido-2-(1'-piperazinyl)-pyrazine hydrochloride
29	3-Hydroxypyrazincarboxamide	3-Carbamoyl-2-(1'-piperazinyl)-pyrazine hydrochloride
30	3-Hydroxy-6-methyl-pyrazincarboxamide	3-Carbamoyl-5-methyl-2-(1'-piperazinyl)-pyrazine hydrochloride
31	5,6-Diphenyl-3-hydroxy-pyrazincarboxamide	3-Carbamoyl-5,6-diphenyl-2-(1'-piperazinyl)-pyrazine hydrochloride
32	3-Methyl-5-phenyl-pyrazinol	3-Methyl-5-phenyl-2-(1'-piperazinyl)-pyrazine hydrochloride

EXAMPLE 33.

2-(3'-Carbethoxy-1'-piperazinyl)-pyrazine hydrochloride

The title compound is prepared similarly to Example 1 by substituting 2-chloropyrazine for 2,6-dichloropyrazine and 2-carbethoxypiperazine for piperazine.

EXAMPLE 34.

2-(3'-Carboxy-1'-piperazinyl)-pyrazine hydrochloride

A solution of 5 g. of 2-(3'-carbethoxy-1'-piperazinyl)-pyrazine hydrochloride in 50 ml. of 1N hydrochloric is stirred at reflux for two hours. After concentration under reduced pressure at 50°, absolute ethanol is added to the residue and the solution is reconcentrated. The addition of ethanol and concentration are repeated two more times. The residue is recrystallized from a mixture of methanol and ethyl acetate to give 2-(3'-carboxy-1'-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 35.

6-Methylthio-2-(1'-piperazinyl)-pyrazine hydrochloride

A mixture of 0.13 mole of sodium methylmercaptide (prepared from 3.12 g. sodium hydride and an excess of methyl mercaptan), 20 g. (0.13 mole) of 2,6-dichloropyrazine and 200 ml. benzene is heated at reflux for 24 hours, cooled and washed twice with 50 ml. water. The benzene layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Distillation of the residue gives 2-chloro-6-methylthiopyrazine.

To a solution of 10 g. piperazine in 150 ml. of 2-butanol is added 8.03 g. (0.050 mole) of 2-chloro-6-methylthiopyrazine. After heating at reflux under nitrogen for 6 hours, solvent is removed under reduced pressure and the residue partitioned between dilute sodium hydroxide solution and benzene. The benzene extract is washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue is dissolved in ethanol and acidified with anhydrous ethanolic-hydrogen chloride solution. The precipitated salt is recrystallised from a methanol-ethyl acetate mixture to give 6-methylthio-2-(1'-piperazinyl)-pyrazine hydrochloride.

The following examples describe alternative synthetic routes for the preparation of 6-chloro-2-(1-piperazinyl)pyrazine hydrochloride.

EXAMPLE 36.

A. From N,N'-bis-(6-chloro-2-pyrazinyl)-piperazine

(a) A mixture of 15.0 g. (0.10 mole) of 2,6-dichloropyrazine, 4.3 g. (0.050 mole) of anhydrous piperazine, and 20.4 g. (0.20 mole) of triethylamine in 200 ml. n-butanol is heated at reflux for 3 hours. The mixture is concentrated under reduced pressure and the residue partitioned between 1 N aqueous sodium hydroxide solution and benzene. The combined benzene extracts are washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to N,N'-bis-(6-chloro-2-pyrazinyl)-piperazine.

(b) The N,N'-bis(6-chloro-2-pyrazinyl)-piperazine from the preceding step is stirred at reflux for 8 hours in 500 ml. of concentrated hydrochloric acid. After concentrating to dryness under reduced pressure, the residue is recrystallized from 95% ethanol to give 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

B. From 2-chloro-6-(4-formyl-1-piperazinyl)-pyrazine

(a) 2,6-Dichloropyrazine, 7.5 g. (0.050 mole), is added to 10 g. of N-formyl-piperazine in 100 ml. of acetonitrile and the mixture heated at reflux for 2 hours. After concentrating under reduced pressure, the residue is partitioned between 2 N sodium carbonate solution and benzene. The benzene layer is removed, washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is essentially pure 2-chloro-6-(4-formyl-1-piperazinyl)-pyrazine.

(b) The N-formyl derivative, 2.0 g. (8.82 mmole) is added to 100 ml. concentrated hydrochloric acid and stirred at reflux for 10 hours. The solution is concentrated to a small volume, diluted with water, and cooled to give 6-chloro-2-(1-piperazinyl)pyrazine hydrochloride.

C. From 6-chloro-2-(4-methyl-1-piperazinyl)-pyrazine

(a) A mixture of 30 g. (0.20 mole) of 2,6-dichloropyrazine and 40 g. (0.40 mole) of N-methylpiperazine in 200 ml. of n-butanol is stirred at reflux for 6 hours. The reaction mixture is concentrated under reduced pressure. After addition of 200 ml. of saturated sodium carbonate solution to the residue, the product is extracted into benzene. The benzene extract is washed with water, dried (magnesium sulfate), filtered and concentrated to give 6-chloro-2-(4-methyl-1-piperazinyl)-pyrazine.

(b) The 4-methylpiperazine derivative from the previous step is treated with 0.2 mol of cyanogen bromide in toluene at 0° and the resulting mixture heated 4 hours at reflux and cooled. The mixture is concentrated *in vacuo* and treated with 100 ml. of 6 N aqueous hydrochloric acid for 18 hours at reflux and cooled. The

precipitated product is recrystallized further from 95% ethanol to give 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 37.

A stream of chlorine gas is bubbled through a well stirred solution of (1.0 mol) of 2-(1-piperazinyl)-pyrazine hydrochloride in 1 l. of glacial acetic acid at 100°C. until reaction is complete. After concentrating under reduced pressure, the residue is dissolved in 600 ml. of 0.5 N aqueous hydrochloric acid, seeded with an authentic sample of 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride, concentrated and cooled. The precipitated solid is recrystallized further from 95% ethanol to give pure 6-chloro-2-(1-piperazinyl)pyrazine hydrochloride.

EXAMPLE 38.

The 1- or 4-N-oxide of 6-chloro-2-(1-piperazinyl)-pyrazine, 21.5 g. (0.100 mole), is dissolved in 200 ml. of glacial acetic acid. The solution is warmed to 85°C., saturated with anhydrous hydrogen chloride gas and treated with a stream of sulfur dioxide at this temperature for 1 hour. The acetic acid is removed under reduced pressure and the residue recrystallized from 95% ethanol to give 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 39.

A. A mixture of 5.8 g. (0.045 mole) of 2-amino-6-chloropyrazine, 4.68 g. (0.015 mole) of bis-(2-bromoethyl)-amine hydrobromide and 25 ml. of 2-butanone is heated at reflux for 10 hours. After cooling at 0°C. for 15 hours, the mixture of hydrobromide salts is removed by filtration and dissolved in 25 ml. water. The aqueous solution is made basic to pH 10 with 10% sodium hydroxide solution. The crude product is extracted into 100 ml. benzene and washed with two 25-ml. portions of water. The benzene extract is dried over anhydrous magnesium sulfate, filtered and concentrated to give the free base of 6-chloro-2-(1-piperazinyl)-pyrazine. Conversion to the hydrochloride salt with anhydrous ethanolic hydrogen chloride and recrystallization from 95% ethanol gives 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

B. (a) A mixture of 15.0 g. (0.10 mole) of 2,6-dichloropyrazine and 19.0 g. (0.20 mole) of iminodiacetonitrile in 200 ml. of 2-butanol is heated at reflux for 6 hours. After concentrating under reduced pressure at 55°C., the residue is partitioned between 200 ml. of 2 *N* sodium carbonate solution and 200 ml. of benzene. The aqueous layer is re-extracted with 100 ml. benzene. The combined benzene extracts are dried (sodium sulfate), filtered and concentrated under reduced pressure at 45°C. to give 6-chloro-2-(biscyanomethylamino)-pyrazine.

(b) To a solution of 2.5 g. (0.012 mole) of 6-chloro-2-(biscyanomethylamino)-pyrazine in 500 ml. tetrahydrofuran is added 0.048 mole of borane in tetrahydrofuran at 0°C. The mixture is warmed to 25°C. for 3 hours and then to reflux for 1 hour and cooled to 0°C. Glacial acetic acid (0.072 mol) is added at 0° and the mixture stirred at 0—28° until hydrogen evolution ceases. The solvent is removed *in vacuo* and the residue partitioned between $CHCl_3$ and 2 N aqueous sodium hydroxide. After drying the organic phase over anhydrous sodium sulfate, filtering and concentrating, the residue is converted to the hydrochloride salt with anhydrous ethanolic hydrogen chloride. Recrystallization from 95% ethanol gives 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 40.

A. A suspension of 18.7 g. (0.10 mole) of 5-amino-3-chloro-2-carbomethoxy-pyrazine in a mixture of 114 ml. 48% hydrobromic acid and 30 ml. acetic acid is cooled to 0°C., stirred and treated with a solution of 15 ml. bromine in 30 ml. acetic acid over a period of 45 minutes. A solution of 17.4 g. (0.10 mole) of sodium nitrite in 40 ml. water is then added while maintaining a reaction temperature of 0°C. Stirring is continued for 30 minutes and excess bromine is destroyed by the dropwise addition of 150 ml. of a 30% aqueous solution of sodium bisulfite. The product is removed by filtration, washed with water and recrystallized from an ethyl acetate-hexane mixture to give 5-bromo-3-chloro-2-carbomethoxypyrazine.

B. A mixture of 10.0 g. (0.040 mole) of 5-bromo-3-chloro-2-carbomethoxy-pyrazine, 6.9 g. (0.080 mole) of anhydrous piperazine and 100 ml. acetonitrile is heated at reflux for 2 hours. The mixture is concentrated under reduced pressure and the residue partitioned between 2 N sodium carbonate solution and benzene. The benzene extract is washed with water, dried (anhydrous magnesium sulfate),

filtered and concentrated under reduced pressure. The residue is converted to the hydrochloride salt with ethanolic hydrogen chloride solution and recrystallized from ethanol-ethyl acetate to give 2-carbomethoxy-3-chloro-5-(1-pip razinyl)-pyrazine hydrochloride.

C. A solution of 5.8 g. (0.023 mole) of the methyl ester in 50 ml. of 1 N hydrochloric acid is heated at reflux for 5 hours. After concentrating to a small volume under reduced pressure, the residue is dried further by azeotroping with ethanol. The solid 2-carboxy-3-chloro-5-(1-piperazinyl)-pyrazine hydrochloride is removed by filtration and dried.

D. A suspension of 5.0 g. (0.018 mole) of the hydrochloride of 2-carboxy-3-chloro-5-(1-piperazinyl)-pyrazine hydrochloride in 50 ml. of tetralin is stirred at reflux for about 1 hour until evolution of carbon dioxide is complete. The hot mixture is extracted with two 50 ml. portions of 0.5 N aqueous hydrochloric acid. The aqueous extracts are combined, concentrated and cooled. The precipitated 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride is removed by filtration and dried.

EXAMPLE 41.

A. Solid 6-methoxy-2-(1-piperazinyl)-pyrazine dihydrochloride, 38.8 g. (0.20 mole) is added in portions over 1 hour to 300 ml. of rapidly stirred phosphorus oxychloride at 40—50°C. After addition is complete, the mixture is stirred at reflux for 1 hour, cooled and concentrated to dryness under reduced pressure. The residue is recrystallized first from a small volume of water, then from 95% ethanol to give 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

B. (a) A mixture of 100 g. (0.77 mole) of 2-chloro-pyrazine-1-oxide and 17.2 g. (2.0 mole) of anhydrous piperazine in 1 liter of 2-butanol is heated at reflux for 6 hours. After concentrating under reduced pressure, the residue is dissolved in a mixture of 1 liter of 2 *N* sodium carbonate solution and 1 liter of chloroform. The aqueous layer is re-extracted two times with fresh chloroform. The combined chloroform extracts are dried over anhydrous sodium sulfate, filtered and concentrated. The residue is treated with excess of ethanolic hydrogen chloride and recrystallized from 95% ethanol to give 2-(1-piperazinyl)-pyrazine-1-oxide hydrochloride.

(b) To 300 ml. of cold redistilled phosphorus oxychloride, 21.7 g. (0.10 mole) of 2-(1-piperazinyl)-pyrazine-1-oxide hydrochloride is added in several portions. The mixture is warmed and after a vigorous reaction has subsided is stirred at reflux for an additional hour. Excess of phosphorus oxychloride is removed under reduced pressure. The residue is poured cautiously onto 200 g. crushed ice. The solution is neutralized with cold 5 *N* sodium hydroxide solution and extracted with chloroform. The combined chloroform extracts are dried over anhydrous sodium sulfate, filtered and concentrated. The residual oil is converted to the hydrochloride salt with ethanolic hydrogen chloride and recrystallized from 95% ethanol to give 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 42.

To a solution of 21.3 g. (0.10 mole) of 6-chloro-2-(3-oxo-1-piperazinyl)-pyrazine in 200 ml. tetrahydrofuran is added 0.12 mole of borane in tetrahydrofuran at 0°C. The mixture is warmed to 25°C. for 3 hours and than to reflux for 1 hour and cooled to 0°C. Glacial acetic acid (0.6 mole) is added at 0°C. and the mixture is stirred at 0—25°C. until hydrogen evolution ceases. The solvent is removed *in vacuo* and the residue partitioned between $CHCl_3$ and 2 N aqueous sodium hydroxide. After drying the organic phase over anhydrous sodium sulfate, filtering and concentrating, the residue is converted to the hydrochloride salt with anhydrous ethanolic hydrogen chloride. Recrystallization from 95% ethanol gives 6-chloro-2-(1-piperazinyl)-pyrazine hydrochloride.

EXAMPLE 43.

PREPARATION OF CAPSULE FORMULATION

Ingredient	Milligrams per Tablet
6-Chloro-2-(1'-piperazinyl)-pyrazine hydrochloride	6
Starch	87
Magnesium stearate	7

The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 100 milligrams per capsule.

EXAMPLE 44.

PREPARATION OF TABLET FORMULATION

Ingredient	Milligrams per Tablet
6-Chloro-2-(4'-acetyl-1'-piperazinyl)-pyrazine	12
Lactose	200
Corn starch (for mix)	50
Corn starch (for paste)	50
Magnesium stearate	6

The active ingredient, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in water at a ratio of 10 grams of corn starch per 80 milliliters of water and heated with stirring to form a paste. This paste is then used to granulate the mixed powders. The wet granules are passed through a No. 8 screen and dried at 120°F. The dry granules are passed through a No. 16 screen. The mixture is lubricated with magnesium stearate and compressed into tablets in a suitable tableting machine. Each tablet contains 12 milligrams of active ingredient.

EXAMPLE 45.

PREPARATION OF ORAL SYRUP FORMULATION

Ingredient	Amount
5-Chloro-2-(1'-piperazinyl)-pyrazine	25 mg.
Sorbitol solution (70% N.F.)	40 ml.
Sodium benzoate	150 mg.
Sucaryl	90 mg.
Saccharin	10 mg.
Red Dye (F.D. & Co. No. 2)	10 mg.
Cherry Flavor	50 mg.
Distilled water qs to	100 ml.

The sorbitol solution is added to 40 milliliters of distilled water and the active ingredient is suspended therein. The sucaryl, saccharin, sodium benzoate, flavor and dye are added and dissolved in the above solution. The volume is adjusted to 100 milliliters with distilled water.

Other ingredients may replace those listed in the above formulation. For example, a suspending agent such as bentonite magma, tragacanth, carboxymethylcellulose, or methylcellulose may be used. Phosphates, citrates or tartrates may be added as buffers. Preservatives may include the parabens or sorbic acid and other flavors and dyes may be used in place of those listed above.

EXAMPLE 46.

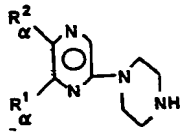
On the day immediately preceding the test day (control day) the food consumption is measured for groups of from 7 to 10 rats allowed access to food for only 2 hours per day. On the next day (test day) the rats are injected i.p. with different dose levels of the test compound 3 minutes prior to commencement of the 2-hour feeding period. Food consumption on the test day is then measured and compared (paired t-test) with consumption on the control day. The results using representative compounds of the present invention are set forth in the following table.

Compound of Example	Dose mg/kg i.p.	Grams Eaten on Control Day	Grams Eaten on Test Day
1	1.5	14.2 ± 2.5^a	7.5 ± 2.0^a
2	12.0	19.3 ± 2.2	14.1 ± 2.2
3	6.0	15.9 ± 2.9	5.5 ± 2.2
4	3.0	14.0 ± 2.3	8.3 ± 2.1
5	6.0	12.3 ± 4.6	3.1 ± 0.9

[a] Standard Deviation.

WHAT WE CLAIM IS:—

1. A compound of the formula:



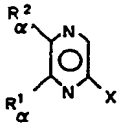
or pharmaceutically acceptable salt or N-oxide thereof, where

R_α^1 is hydrogen, halogen, trifluoromethyl, C_{1-4} alkoxy, C_{2-6} dialkylamino or phenylthio, and

R_α^2 is hydrogen, halogen, or phenyl, with the proviso that R_α^1 and R_α^2 are not both hydrogen.

2. A compound according to claim 1 wherein R_α^1 is chlorine and R_α^2 is hydrogen.

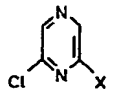
3. A method of preparing a compound of claim 1 which comprises reacting a pyrazine of the formula:



where X is halogen, C_{1-5} alkylsulfonyl, phenylsulfonyl, C_{1-5} alkylsulfinyl or phenylsulfinyl, with piperazine at a temperature of from 15°C. to 90°C. until a substantial amount of compound of claim 1 is obtained.

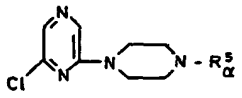
4. A method according to claim 3 in which the reaction takes place under inert atmosphere for from 0.5 to 6 hours.

5. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises treating a compound of formula:



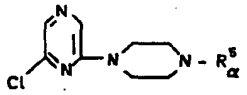
where X is halogen, C_{1-5} alkylsulfonyl, phenylsulfonyl, C_{1-5} alkylsulfinyl or phenylsulfinyl with piperazine at a temperature in the range 15 to 90°C.

6. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises hydrolysing a compound of formula:



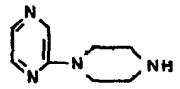
where R^5_α is a heterocycle, alkanoyl, aroyl, alkoxycarbonyl, alkenoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, cyano, carbamoyl, N-alkylcarbamoyl, or N-arylcarbamoyl.

7. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises catalytically hydrogenolysing a compound of formula:

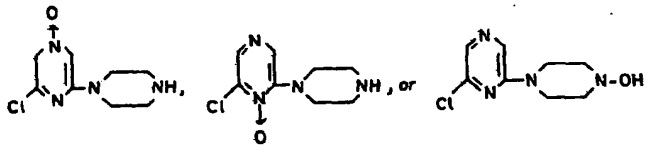


where R^5_α is carboaralkoxy, or aralkyl.

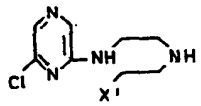
8. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises chlorinating a compound of formula:



9. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises reducing a compound of formula:

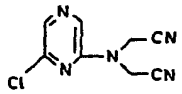


10. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises cyclizing a compound of formula:



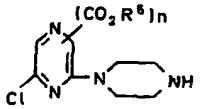
in which X' is a displaceable group or atom.

11. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises reducing the compound of formula:



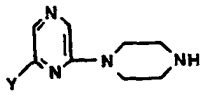
by catalytic hydrogenation or the use of a hydride reducing agent.

12. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises hydrolysing and/or heating a compound of formula:



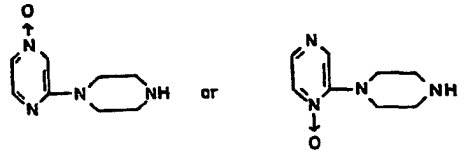
where n is 1 or 2 and R^6 is hydrogen, alkyl or aralkyl.

13. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises chlorinating a compound of formula:

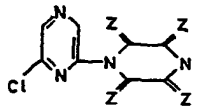


where Y is hydroxy or alkoxy.

14. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises chlorinating a compound of formula:



15. A method of preparing 6-chloro-2-(1'-piperazinyl)pyrazine, that comprises reducing a compound of formula:

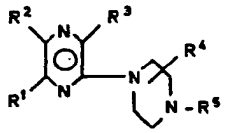


where Z is H_2 or O, at least one Z being O, by catalytic hydrogenation or by means of a hydride reducing agent.

16. A method of preparing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1, 3 to 7, 9, 19, 20, 24 and 36 to 42.

17. A compound as claimed in Claim 1, when prepared by a method as claimed in any one of Claims 3 to 16.

18. A method of decreasing food intake in a mammalian species which comprises administering to a host animal an effective amount of a compound of formula:



in which R^1 is hydrogen, halogen (F, Cl, Br or I), C_{1-3} haloalkyl, C_{1-4} alkoxy, amino, C_{1-7} alkylthio, phenylthio, carbamoyl, (C_{1-4} alkyl)carbamoyl, (C_{1-5} alkoxy)carbonyl, C_{2-6} dialkylamino, phenyl, or phenyl substituted by halogen (F, Cl, Br or I), by C_{1-4} alkyl or by C_{1-3} alkoxy;

R^2 is hydrogen, halogen, C_{1-3} alkyl, cyano, amino, (C_{1-5} alkoxy)carbonyl, carbamoyl, C_{1-4} alkoxy, C_{1-3} haloalkyl, phenyl, or phenyl substituted by halogen;

R^3 is hydrogen, halogen, C_{1-3} alkanoylamino, carbamoyl, phenyl or phenyl substituted by halogen, by C_{1-4} alkyl or by C_{1-3} alkoxy;

R^4 is hydrogen, C_{1-3} alkyl, carboxyl or (C_{1-5} alkoxy)carbonyl; and

R^5 is hydrogen or C_{1-3} alkanoyl;

or an N-oxide or acid-addition salt of such a compound.

19. A pharmaceutical composition in the form of tablets, troches, pills, capsules, elixirs, suspensions, syrups, wafers or chewing gum, comprising a compound as defined in Claim 18 in combination with a pharmaceutically acceptable carrier.

20. A food containing as an added ingredient a compound as defined in Claim 18.

21. A composition containing as active ingredient a non-toxic carrier and a compound as claimed in Claim 1, 2 or 17.

22. A composition as claimed in Claim 21 in a pharmaceutical orally administrable form.

23. A composition as claimed in Claim 22 in the form of tablets, troches, pills, capsules, elixirs, suspensions, syrups, wafers or chewing gum.

24. A composition as claimed in Claim 21, in which the carrier is a food.

25. A composition as claimed in Claim 19, substantially as hereinbefore described in Example 43, 44 or 45.

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